



Harnessing the microbiome to prevent global biodiversity loss

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Global biodiversity loss and mass extinction of species are two of the most critical environmental issues the world is currently facing, resulting in the disruption of various ecosystems central to environmental functions and human health. Microbiome-targeted interventions, such as probiotics and microbiome transplants, are emerging as potential options to reverse deterioration of biodiversity and increase the resilience of wildlife and ecosystems. However, the implementation of these interventions is urgently needed. We summarize the current concepts, bottlenecks and ethical aspects encompassing the careful and responsible management of ecosystem resources using the microbiome (termed microbiome stewardship) to rehabilitate organisms and ecosystem functions. We propose a real-world application framework to guide environmental and wildlife probiotic applications. This framework details steps that must be taken in the upscaling process while weighing risks against the high toll of inaction. In doing so, we draw parallels with other aspects of contemporary science moving swiftly in the face of urgent global challenges.

Five of the nine proposed planetary boundaries, which represent the limits within which humans can safely inhabit the Earth¹, have now been breached due to human activities: climate change, biosphere integrity loss, land-system change, plastic and chemical pollution, and altered biogeochemical cycles². We are now firmly entrenched within a sixth mass extinction event³, with loss in corals, bats, bees and amphibians being the most prominent examples of anthropogenically driven biodiversity loss^{4–6} (Supplementary Fig. 1). Currently, widespread extinction events impair the resilience, function and stability of ecosystems, which impacts our existence^{7–9}, conceptually referred to as ‘One Health’ (that is, the interconnection between people, animals and the environment)^{5,6}.

In the face of such alarming challenges, recent advances in research have indicated the potential of microbiome-based interventions, such as probiotics to protect wildlife and mitigate environmental impacts, and microbiome transplants to restore ecosystems

and improve their resilience^{10–21}. We explore synergies between different disciplines, synthesize basic microbiome engineering and symbiosis concepts, and identify critical challenges and safety issues. Importantly, we provide guidelines for designing and implementing microbiome-based strategies to mitigate biodiversity decline using existing examples. We argue that the consequences of biodiversity loss are so serious that the risk of inaction must be weighed against the risk of taking a less-than-perfect action or even the risk of making things worse. This argument implies that regulatory and safety guidelines must be practical, flexible and stipulated using a case-by-case approach, considering the current state of each host and ecosystem as well as scientific insights. In this regard, we discuss crucial ethical considerations, risks, costs and benefits, and opportunities across multiple fields of microbiome management to synthesize an evidence-based framework to accelerate the practical use of emergent approaches. Finally, we draw parallels to other

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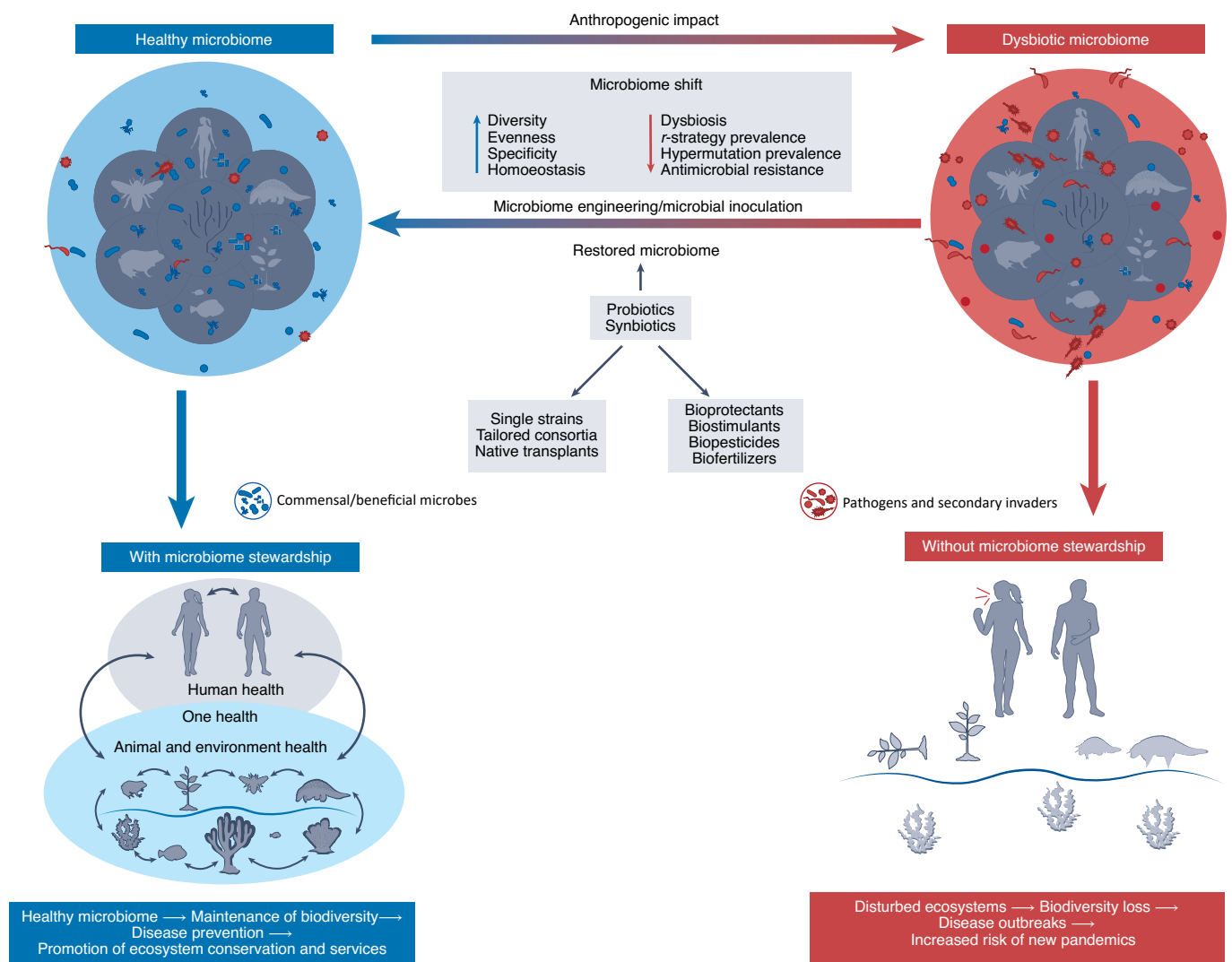


Fig. 1 | Microbiome stewardship as a potential tool to mitigate anthropogenic impacts. Anthropogenic impacts can disturb healthy microbiomes, causing dysbiosis characterized by loss of diversity, evenness and homoeostasis, and increased prevalence of *r*-strategy microbes, hypermutation and antimicrobial resistance. This can result in disturbed ecosystems, the outbreak of pests and pathogens and, thus, increased risk of disease. Microbiome stewardship can exploit the microbiome given that these microbial communities are key members of the holobiont, connect all ecosystem entities, respond rapidly to manipulation with immediate effects and are easier to manipulate than macro-organisms. The use of probiotics or synbiotics is one approach to promote ecosystem functioning and overall one health, avoiding biodiversity loss, pandemics and other impacts while retaining ecosystem services.

fields of applied science moving swiftly in the face of other current and urgent global challenges.

Biodiversity loss in the Anthropocene

One of the primary hallmarks of the Anthropocene is the progressive elimination of species across a wide taxonomic range—from plants to insects, amphibians, birds and mammals^{22,23}. In contrast, relatively little is known about the decline in microbial diversity and its potential consequences²⁴. Symbiotic relationships between eukaryotic hosts and microbes constituting the holobiont or meta-organism^{25,26} are key for organism health and support critical ecosystem functions in all habitats on Earth²⁷. In a healthy organism, host–microbe interactions are sufficiently balanced, with certain microbiome members often buffering against biological or environmental disturbances to maintain homoeostasis and function (Fig. 1). Projecting back, microbial symbionts were drivers of plant terrestrialization in early Palaeozoic land ecosystems²⁸, and co-evolution with their hosts resulted in specific and unique host–microbe interactions and microbial assemblages on Earth²⁹. Consequently,

the loss of multicellular, eukaryotic hosts documented by massive extinction events in the past and today is in all likelihood accompanied by the currently undocumented loss of microbial genetic and metabolic diversity³⁰. Recent studies have described a microbiome signature of the Anthropocene, which is characterized by a shift towards global homogenization, diversity loss, *r*-strategist (that is, fast-growing) microbes and often multiresistant pathogens^{24,31,32}. We posit that such shifts, particularly in host–microbiome associations, are often followed by dysbiosis (that is, the disruption of microbial networks and functions that impact symbiotic relationships within a holobiont)³³ and facilitate disease. Dysbiosis is also associated with severe chronic diseases and long-term biotic stress that are well-documented for humans^{34,35} and crops^{36,37} but remain understudied in wildlife and natural vegetation.

Microbiome stewardship

The treatment and management of microbial disruptions have traditionally focused on administering antimicrobials³⁸, with little consideration for the maintenance of the beneficial constituents

of the microbiome itself. We adopt the term ‘microbiome stewardship’ to underscore that organismal and ecosystem health can be more effectively managed and maintained by monitoring and suitably manipulating the microbiome. Accordingly, the term encompasses the sum of all approaches, methodologies and technologies to understand and, consequently, manipulate microbiome function, with stewardship emphasizing the advocacy and support for science-based management.

Understanding and manipulating microbiome function is a daunting task, given the metabolic and physiological flexibility of microbes to adapt in response to change³⁹. Additionally, our understanding of how to retain or restore a healthy microbiome is often limited⁴⁰, in large part by available technologies and the lack of basic understanding of the ecological mechanisms that govern microbiome assembly, growth and evolution^{39,41}.

Microbiome members that are important for holobiont functioning could be harnessed to rescue threatened host species or ecosystems. Competitive microbial interactions and the host immune response are the proposed mechanisms for enriching community members with antagonistic properties against pathogens. Similarly, microbial relief of holobiont stress has been proposed to rescue hosts subjected to environmental effects^{11–17,21,42–44}. Mechanistically, this involves beneficial microbes that can improve the uptake of nutrients, vitamins and minerals, mitigate toxic compounds, control pathogens, and promote growth and fitness, among other favourable roles⁴⁵. This concept is similar to the pollution-induced tolerance concept introduced by Blanck and Wängberg⁴⁶ in ecotoxicology or the biological control of pathogens widely explored in agricultural systems⁴⁷.

Microbe-mediated disease control is becoming more commonly employed, with microbiome-targeted interventions undergoing development. These efforts have focused on humans and plants, with aquaculture species also receiving increasing attention^{48–50}. In Box 1, we present a detailed summary of the state-of-the-art microbiome stewardship approaches for some of these hosts and the strategies applied to the tailored design of probiotics across holobionts. This tendency towards defined and tailored treatment has existed for many areas (for example, precision farming and personalized medicine)^{51,52}. While some of these strategies work well^{53,54}, many others have failed or demonstrated inconsistent results^{55,56}. These approaches are not necessarily new or exclusive to a specific host^{50,57–59}, and efforts to manipulate the human microbiome date back over a hundred years⁶⁰. The recent elevated interest in this concept is encouraging and includes a focus on wildlife and natural ecosystems^{10–21}.

In general, microbiomes can be managed either by directly applying (1) defined microbes and mixtures/consortia of strains with beneficial properties (probiotics), (2) microbiota transplants, (3) microbiota-active metabolites or (4) mixtures of probiotics and prebiotics (synbiotics), or even indirectly by changing environmental conditions to drive shifts in the microbiome structure and function, turning a dysbiotic holobiont into a healthy one⁵¹. Although the definition of a ‘healthy’ microbiome is still being characterized and debated, on the basis of the available data, we propose a ‘microbiome stewardship’ concept that focuses on the use of probiotics. These approaches and the associated outcomes should be measured against the available alternative treatments and potential associated risks (Fig. 1).

Designing probiotics for microbiome stewardship

Designing probiotic products comprises four steps: discovery, screening and evaluation, formulation and application. This process benefits from an ecological and evolutionary understanding of the target ecosystem and the disrupted factors (with a particular focus on function). This strategy has been used to some extent for microbiome stewardship of the human gut microbiome as a treatment for

Clostridioides difficile infection⁶¹. Disruption of the gut microbiome by antibiotics can lead to *C. difficile* infection due to reduced microbial competition and habitable niches. Microbiome restoration has been performed with faecal microbiota transplantation (FMT), which can re-establish colonization resistance and thus alleviate disease⁶². This paradigm of transplanting complex communities from healthy donors with intact communities to health-compromised recipients with disrupted communities could apply to other organisms and ecosystems.

Specific beneficial microbes or defined mixtures/consortia of strains could also be used to promote the health of a host or ecosystem^{11,13,14}. Probiotic strains for such applications can be discovered from various sources, but ecology-based selection strategies that consider the origin and evolutionary history of strains are suggested to ensure adaptation and functionality. For example, microbes that exhibit inverse associations with pathologies are promising candidates for developing probiotics or defined consortia that can be explored for therapies⁶³.

Probiotic candidates must undergo extensive screening to evaluate their efficacy and mode of action (MOA) following enrichment and isolation. The effectiveness of a multifaceted screening approach to obtain the ‘best’ microorganisms from natural bioresources has been demonstrated⁶⁴. Microbial transplants from resilient wild plants, mosses and lichens were used and their colonization on crop roots and leaves were tracked to re-isolate promising probiotic candidates⁶⁴. Moreover, a comprehensive set of assays was developed to determine the capability of isolates to protect against different sources of stress and MOA studies were also performed⁶⁴. The inclusion of multi-omics technologies in the screening process is particularly valuable to assess the full potential of candidate strains⁵⁷, including their MOA⁶⁵ and potential off-target or side effects⁵¹. Consortia that combine microbes with different MOAs (that is, ‘helper strains’) and metabolic boosters (that is, compounds that can accelerate/trigger the production of specific metabolites) have also been shown to have higher efficiency than single-strain inoculations⁵¹.

Once data on their activity, genetic profile and interactions with other microbes or the host has been assembled, promising candidates or consortia can be chosen for a formulation process. In some cases, stabilizing additives are used to provide long shelf life. Subsequent large-scale production and registration are the remaining important hurdles for probiotic development. While the focus of the probiotic design is often the efficacy of the strains, other important aspects, such as safety and risk assessment, knowledge translation and ethics, must be considered during the early stages of development.

Risk and safety considerations of microbiome stewardship

Risk assessment is an important requirement that is currently among the greatest bottlenecks when registering a novel probiotic: they are costly, time-consuming and often inefficient in considering the specific features of each bioproduct⁶⁶.

The regulation of bioproducts for microbial management varies between countries and areas of application, and are not compatible with each other. For example, in the United States, the Food and Drug Administration developed a safety evaluation framework that may assign microbial products the ‘Generally Recognized as Safe’ status before being marketed (<https://www.fda.gov/home>). However, the European Union Food Safety Authority uses a different framework based on a list of microbial species that may be considered safe depending on their taxonomic affiliation, existing scientific knowledge, pathogenicity and virulence, and safety for the environment. However, several microbial species still require full safety assessment and the number of included species is limited. Thus, most environmental probiotic candidates require a full safety assessment as they are not included in this list. This is further complicated by the fact that microbial products rely on living

Box 1 | Examples of commonly studied hosts receiving probiotics*Humans*

Probiotics for humans date back to 1907, when *Lactobacilli* were suggested to increase longevity⁶⁰. Towards the end of the twentieth century, the concept of probiotics emerged⁹¹ and was applied to intestinal and urogenital health⁹². Interest in manipulating microbes and their metabolic readouts, including probiotics, prebiotics (that is, substrates for beneficial microbes), synbiotics (microbes and growth stimulants) and postbiotics (microbial metabolites)^{93–96}, as well as FMTs, has since increased considerably. Examples of successful microbiome manipulation in humans includes FMT for *Clostridioides difficile* infection and the use of probiotics to prevent and treat necrotizing enterocolitis in infants^{97,98}.

Plants

Beneficial microorganisms represent one of the fastest-growing sectors in agronomy, with a compound annual growth rate of 15% to 18%. Various plant probiotic formulations are currently in use and are categorized according to mode of action: biopesticides (direct activity toward pests and pathogens, which are segmented by the target into bioherbicides, bioinsecticides and biofungicides), biofertilizers (nutrient provision for plants) and biostimulants (direct support of plant growth). The majority of products comprise strains native to plants, namely *Azospirillum*, *Bacillus*, *Beauveria*, *Coniothyrium*, *Pseudomonas*, *Trichoderma* and *Rhizobium*⁶⁵. New products will probably be needed to overcome the challenges of climate change, weed and insect infestations, poor soil quality, postharvest spoilage and the growing human population. Another emerging approach is the restoration or protection of extinct or endangered native vegetation and specific wild plants through native mycorrhizal transplants⁹⁹.

Aquaculture

Chemotherapeutic agents, particularly antibiotics, have been among the primary treatments used in aquaculture disease management^{100–102}, contributing to the emergence of antibiotic-resistant bacteria¹⁰⁰. Restrictions on their use have been implemented in some countries to halt the dissemination of these bacteria and to reduce the negative effects of residual antibiotics in aquaculture products¹⁰³. Potential alternatives to prevent disease outbreaks include vaccines and probiotics (Gram-negative or Gram-positive bacteria, yeasts, bacteriophages or unicellular algae)^{50,58,59,104–106}. Currently, a lactic acid bacterium-based product (Bactocell, a feed formulation prepared from the Gram-positive species *Pediococcus acidilactici*)¹⁰⁷ is on the market, and work on the commercial production of a Gram-negative Alphaproteobacteria from the *Roseobacter* group, particularly the species *Phaeobacter inhibens*, is underway⁵⁰. However, the exact mechanisms by which such aquaculture probiotics work are unknown, which has led to new initiatives that base the selection of strains on the mode of action.

Honey bees

Bees are critical pollinators for a wide range of agricultural processes that form global food supplies, but their population has undergone a catastrophic decline over the past decade¹⁰⁸. Bee microbiome composition can be a useful indicator of the overall colony health status, and these microbial communities can confer colonization resistance against parasites, inhibit entomopathogenic tissue invasion and improve nutrient assimilation from the diet¹⁰⁹. To improve resistance to infection during active seasons, beekeepers frequently employ antimicrobials as a prophylactic measure to suppress opportunistic bacterial and fungal pathogens.

Recently, strains of *Lactobacillus* spp. have demonstrated the capacity to attenuate negative effects associated with antibiotic use by stabilizing core microbiota dynamics and preventing the overgrowth of opportunistic pathogens¹⁷. Several studies on bees or other model insects have demonstrated the strain-specific benefits of *Lactobacillus*, *Apilactobacillus* and *Pediococcus* spp. for increasing host survival against single or combinatorial stressors of infection and pesticide exposure^{20,21,110,111}. Together with a high safety profile, this suggests that probiotic lactobacilli could offer a cost-effective and convenient solution to mitigate two of the major factors responsible for bee population decline.

Corals

Coral reefs have been increasingly challenged by the rate and severity of global change and the inability of their foundational species, reef-building coral, to cope with detrimental effects^{112–114}. Microbiome-based interventions are promising because they could act on short timescales^{115,116}. Desired beneficial roles of coral microbiome members have recently been proposed and summarized^{117,118}, together with an experimental framework to identify coral probiotic strains and to reveal mechanisms of action^{11,13,117,118}. Several approaches of microbiome stewardship aiming to improve coral resistance to external stressors or bioremediation (for example, through elimination of the pollution effects of oil spills) have already been successfully proven in laboratory trials with different types of coral and bacterial species (for example, *Pseudoalteromonas* sp., *Cobetia* sp., *Halomonas* sp., *Bacillus* sp. and *Brachyбактерium* sp.)^{10–14}. Despite the challenges of applying microbes to surfaces beneath the saltwater ocean, coral microbiomes have been manipulated ex situ through the introduction of probiotic strains by incubation, topical application^{11,13,14,119,120} or direct feeding¹²¹. Microbiome transplantation using resistant donor corals from the wild has also demonstrated thermal protective effects on coral populations¹⁰, such as increased growth¹²⁰ and reduced stress responses under heat (including mortality evasion following thermal stress bleaching)^{11,13,119}, oil exposure^{12,14} and pathogen challenges^{11,116}, all of which are accompanied by microbiome restructuring. Given their associations with a complex microbiome^{39,122}, corals may represent a particularly good system to prove the capacity of microbiome stewardship to reverse organismal and ecosystem decline.

Amphibians

Amphibians perform essential roles in food webs and provide ecosystem services, but global population declines and extinctions include over 500 species^{123,124}. In particular, the invasive chytrid fungi *Batrachochytrium dendrobatidis* and *B. salamandrivorans* are emerging pathogens of urgent concern. Work in Panama has indicated signs of recovery for several amphibian species seriously affected by chytridiomycosis⁴³. This work demonstrated that, while pathogen virulence did not change, mucosal skin defences were higher after disease emergence⁴³. This example of resilience may provide strategies for overcoming environmental disturbance. The use of probiotic bacteria, including¹⁶ *Janthinobacterium lividum*⁴⁴, *Serratia* spp.⁴², *Pseudomonas reactans*¹²⁵, *Bacillus* sp. and cocultures^{125,126}, *Stenotrophomonas* sp. and others^{16,127}, for amphibian disease mitigation has been investigated. Skin microbiome transplants from disease-resistant to disease-susceptible hosts represents another research avenue^{128,129}. Microbes that function via volatile organic compounds are increasingly studied in white-nose syndrome in bats¹³⁰ and are being translated to snake fungal disease¹³¹ and amphibian chytridiomycosis systems¹³².

organisms that themselves have complex and ever-changing physiologies. Although multi-omics technologies often allow us to obtain detailed insight into the potential safety of probiotics for environmental applications, the current lack of a consensus and globally recognized framework for safety assessment still constitutes a major bottleneck in their development.

We believe that an extensive network of collaboration between research, industry and regulators is required to resolve these issues. Integrating microbiome-based concepts, as well as improving and adapting assays to evaluate the effects of new candidate probiotics on living systems offer novel possibilities for efficient risk assessment^{51,66}. A more flexible, science-based system is needed to evaluate risks associated with the use of specific probiotics, where each situation will be evaluated through a case-by-case assessment, as detailed in Fig. 2. Whole-genome sequencing can contribute to understanding a candidate's mode of (inter)action in detail and detecting genes encoding bioactive metabolites, virulence and antimicrobial resistance. Detecting genes of interest is especially critical if present on mobile genetic elements. However, basing the risk assessment only on genomic traits or inferred functions is probably insufficient due to other crucial factors (for example, epigenetic patterns). Therefore, assessments should be supplemented with additional investigations and methods.

Combining ecological, genomic, transcriptomic and physiological data is of scientific value and should be included as much as possible for research on probiotic candidates. However, stipulating clear criteria for which features require investigation for a given probiotic application is challenging, and consideration must be given to the primary outcome. We suggest that knowledge-based assessments on a case-by-case basis using experimental data on microbe behaviour are necessary for environmental microbiome stewardship to counterbalance all aspects discussed above. Notably, such broadly defined individual assessments could represent an even longer process that is difficult to regulate. By comparison, a clear and universal framework that includes a fair, flexible and straightforward roadmap to follow would be more beneficial. This flexible framework should include experimental evaluations of the risks and benefits of using probiotics. In addition, the inherent risks and costs associated with inaction must be considered, as they create the opportunity to select, test and validate potentially innovative and efficient probiotics for environmental applications that current legislations would otherwise prohibit.

Lessons learned from global challenges

We should assess when rapid action is critical and would justify potential and calculated risks, as described in Fig. 2. The knowledge-based assessments of risk outlined above could benefit from an integrative analysis of the use of probiotics for different hosts, delivery methods and quick bench-to-host pathways. The rapid development of multiple vaccines against SARS-CoV-2 is an example of science moving swiftly in response to a medical emergency. Global efforts bridging stakeholders, scientists, and the public and private sectors greatly accelerated these developments, as well as adaptations in legislation, licensing and authorization systems (rapid emergency use authorization), and risk assessment systems, moving from long-term passive/active to real-time safety surveillance. In this emergent framework, rare adverse effects from vaccines were deemed acceptable considering the risk–benefit considerations to immunize most of the human adult population^{67,68}.

As another example, while FMTs have been described for many years, they have not yet been proven safe beyond doubt and adverse effects, although rare, have been reported. Despite this, they are now regularly applied to treat human disease^{69,70}. For *C. difficile* infections, the gain of curing⁷¹ most patients (up to 90%) facing life-threatening diseases must be carefully weighed against the risk of rare but serious adverse outcomes, as reported

when one patient died as a result of multidrug-resistant pathogens being transplanted⁷². In these cases, additional precautions, such as implementing multidrug-resistant strain screening or reassessing microbiota components in donor stool, must be immediately developed to avoid such unacceptable risks. A further illustration of microbiome stewardship for the greater good is manipulation of the bacterial symbiont *Wolbachia* in insect vectors for human disease control (for example, to prevent the spread of dengue, yellow fever or malaria by mosquitoes or other insects)^{73,74}. Despite the need for improvements, all these examples had known and unknown risks at the time of application, but their benefits outweighed the concerns, and inaction would have left a heavy toll in terms of human mortality and morbidity.

Ethical considerations and the inherent risk of inaction

Recent climate-related events, including extremely high temperatures in the Arctic and Antarctic regions⁷⁵, devastating fires in the Amazon Rainforest, Australia and North America^{76–78}, and the massive loss of coral reefs²³ underscore the fact that the duty of environmental stewardship is not an abstract ideal but a concrete imperative for humankind. The stewardship of biodiversity is a collective duty as the planet's ecosystems are strongly interdependent and the integrity of each of these systems is a necessary condition for sustaining life. Therefore, the highest priorities are to restore and conserve threatened ecosystems.

Some may consider microbiome management ethically challenging given the potential effects on other ecosystem members being modified or on the downstream food chain. For example, would using probiotic strains on honey bees result in irreversible alterations to flowering plant microbiota, or would the application of microbes to restore coral reefs affect the fish food chain and, ultimately, humans? Could environmental damage be triggered by such manipulation?

Such ecosystem interventions imply major challenges for assessing risks and benefits, with substantial implications for decision making, responsibility, accountability and governance. One potential risk is the loss of native diversity (for example, if a single probiotic strain takes over an inherent function). This is minimized by niche opportunity and environmental traits that shape microbial diversity (that is, probiotics establishment is rare and seems to be controlled by the host¹³ or by the availability of nutrients and conditions⁷⁹ that triggered impact mitigation). However, this potential drawback should not be ignored and must be evaluated on the basis of the available alternatives.

It is also important to consider that, in some cases, not using probiotic applications may still result in losing native diversity and permit the spread of pathogens, causing major environmental damage. Engineering the environment to support a 'healthy' microbiome is an alternative approach to administering selected probiotics. This might include using prebiotics or beneficial bacteria isolated from the target environment, cultivated at scale and re-introduced into the system. These approaches might lower the risk of losing native diversity compared with administering genetically modified or exogenous strains⁴¹. Another potentially innovative approach would be to use bacteriophages to replace antibiotics and target specific, non-beneficial, microbes^{80,81}.

One critical question that remains is who should decide on the initiation of field trials to test probiotics for environmental applications? For instance, the local or regional communities should be fully informed and involved during the early stages of an intervention, especially if an application remains local (for example, due to species-specific constraints). However, any alterations could ultimately spread globally to all members of that host species, creating an ethical conundrum: who makes the initial decision and can thus be held responsible? How can ecosystem interventions be justified? How can balanced information be provided? These complex

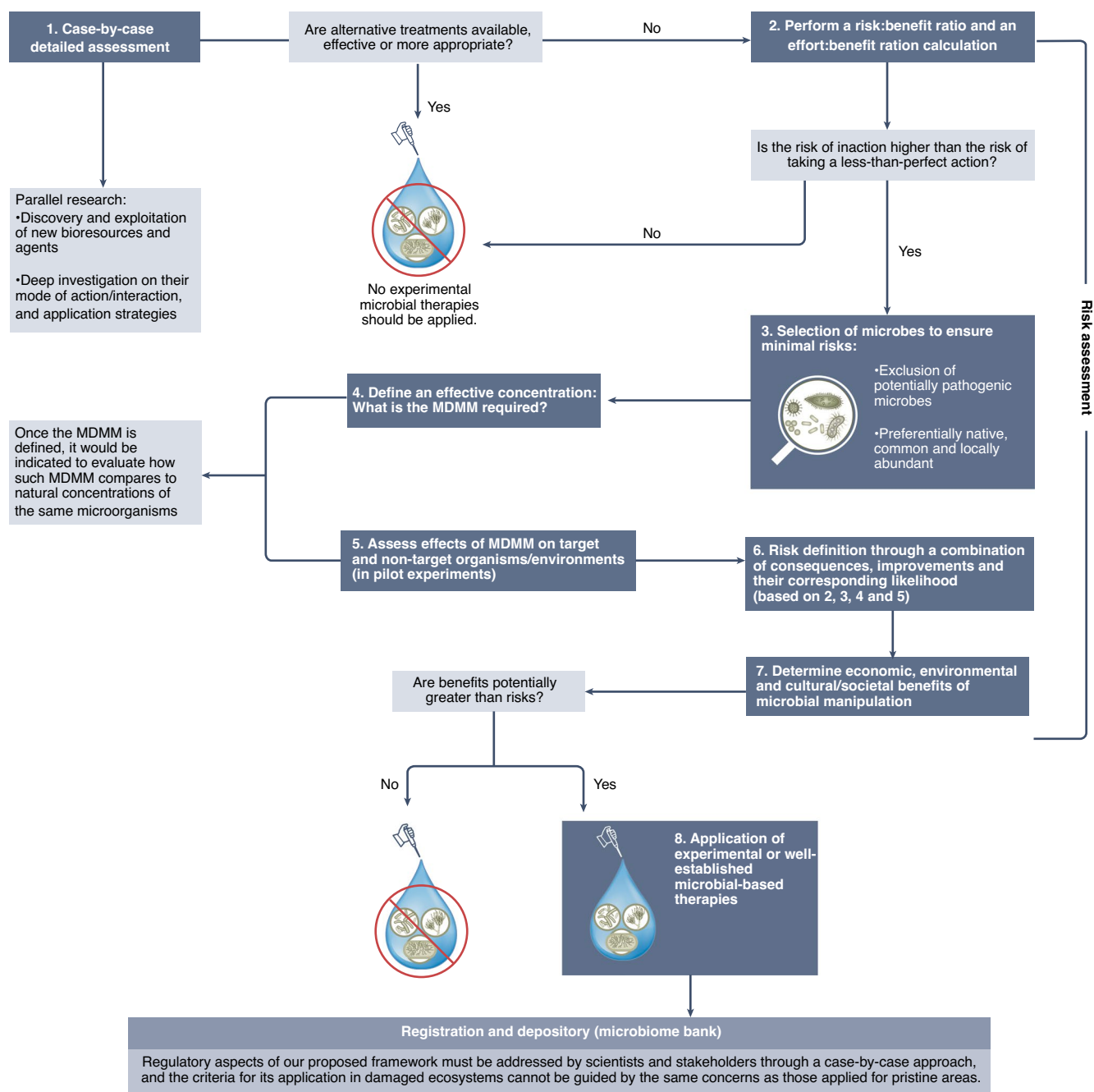


Fig. 2 | Proposed evidence-based framework for microbiome stewardship. The science-based flexible framework includes clear ethical and environmental safety management considerations for developing and implementing probiotics for applications to the environment in a case-by-case approach. The proposed steps could be followed sequentially or in combination and include the specific aspects that need to be considered for the selection and application of probiotics for wildlife. We highlight that risk assessment is the first step, that it should also weigh the risk of inaction against the need for rapid action and that the selection of probiotics should follow a science-informed exclusion of potential pathogens. The framework also suggests an overall survey on the application regime and potential side effects, as well as parallel research to improve our knowledge on the mechanisms driving host–microbiome interactions.

ethical questions must be part of a global debate with all relevant stakeholders. Decisions must be based on broad scientific assessments (for example, peer-reviewed data, scientific networks and so on) and community consultations aligned with international regulations agreed upon in a binding manner, ideally with control instances established (for example, in the form of independent scientific entities that inform governments).

Ethical justifications for novel interventions have a stronger case if the intervention is a last resort, underscoring the ethical imperative to avoid these desperate situations. In addition, we should

consider whether traditional interventions or alternative treatments, such as antibiotics, fertilizers, pesticides and other potentially harmful agents, may be more hazardous than probiotics.

An evidence-based framework for microbiome stewardship

We argue that clear ethical considerations and environmental safety management are necessary to advance research on probiotics applied to the environment and their primary host target. We propose an evidence-based framework (Fig. 2) for implementing environmental and wildlife probiotics (live microbes administered to

species living in the wild) using elements discussed above, with steps that could be followed sequentially or in combination.

First, a detailed initial assessment of the problem must be undertaken similar to environmental impact assessments, ideally including the ecological and evolutionary understanding of the foundational species or ecosystem functions that can help elucidate the mechanistic basis of the environmental disruption. This assessment should include an examination of existing alternative treatments and the resulting risk–benefit and effort–benefit ratios. For example, if the problem is sewage outflow, well-studied alternatives, such as wastewater treatment plants using membranes, flocculants and activated sludge, could be assessed^{82–85}. Likewise, the widespread application of amoxicillin (a potent, broad-spectrum antibiotic) to control the rapidly spreading stony coral tissue loss disease in the Caribbean^{86,87} could be compared with the harm it can cause versus the outcome of using probiotics.

Second, selecting probiotic strains on the basis of specific traits or functions is crucial to optimize the chance of success and minimize the risks. Any microbial species or strain known to be potentially pathogenic should be automatically excluded unless a convincing argument can be made to consider it. Native, commonly found and abundant commensal species should be preferentially selected unless a compelling case can be made to apply a non-native species. Strain properties should be assessed on the basis of what they are expected to achieve in the target environment. For example, the expected result could be to displace specific pathogens, function as keystone species to establish a base for the recovery of communities, improve host functions (development, immune system and so on) or remove pollutants from a habitat or holobiont system. The interaction of a probiotic organism with existing indigenous species and the surroundings should also be considered.

Third, an effective dosage of the probiotic should be used to achieve the desired effect or outcome with minimal degree of microbiome manipulation (MDMM). Whether this should exceed the native abundance of the beneficial microorganisms that exist when the host site is ‘healthy’ remains to be determined.

Fourth, the probiotic delivery system must be determined. Considerations include shelf life, storage and handling, dispersion when applied to water or other surfaces, time to reach metabolic activities essential for success, target uptake, carrier dissolution or degradation, and the broader effects on other organisms in this niche, plus assessing the overall function of the environment. For example, applying probiotics to a honeybee hive to improve resistance against pathogens should not result in lower pollination rates or damage to certain flowering plants.

Fifth, how an MDMM affects different life stages, non-target organisms and environments should be assessed. This assessment could be performed *in vitro*, accounting for spatial and temporal dilution, using model organisms or, when possible, as pilot experiments in natural ecosystems^{88,89}. On the basis of the data, risks are defined through a combination of measured consequences and the likelihood of occurrence. Consequences must be defined in the context of economic, environmental, cultural and societal values⁴¹. In any case, a definitive, closely monitored pilot study is mandatory before full-scale environmental application. Finally, if the benefits of the target organism are greater than the risks to non-target organisms or the environment, then the application of probiotics should be recommended for full in-field assessment. Both scientists and stakeholders must address regulatory aspects, use a case-by-case approach with the proposed framework and acknowledge that the criteria for application in damaged ecosystems cannot be guided by the same concerns as those applied for pristine areas.

Conclusions and future perspectives

Despite the need for well-exercised caution, there is an increasing understanding that time is of the essence. Microbiome stewardship

is dependent on specific traits, abiotic conditions and goals (for example, whether specific pathogens or beneficial microbes must be eliminated or promoted, respectively). Its scope includes (1) targeted disruption of specific microbes and their metabolic activity, (2) supplementing the host or ecosystem with native or non-native microbes, (3) changing the microbiome by manipulating substrates and (4) reducing host exposure to factors such as antimicrobial toxins or pollutants. Ensuring a sound scientific basis for overseeing these investigations forms an important part of microbiome stewardship, but this takes time, resources and willpower. Unfortunately, time is running out, which is why commitments must be made now, while robust investigation on macro and (especially) micro biodiversity losses, as well as ecosystem function and mechanism, should also be prioritized and supported by targeted funding opportunities.

Numerous challenges are shared across different hosts and environments. In many cases, the current technology is not safer than a microbiome modulation *per se*, for example when the current treatment is antibiotics, which comes with potential risk of failure or multidrug-resistance spread. We argue that the administration of strain-specific microbes, risk-assessed by the best means possible and scientifically characterized, is a safe option with potentially profound benefits.

In conclusion, we emphasize that it is imperative to address the nature and extent of the consequences of continued inaction. Many examples exist where we have failed to treat diseases with a chemical approach and have consequently caused major environmental disruption. The proposed use of beneficial microbes as an alternative is currently hindered by the lack of appropriate risk assessment or ethical frameworks that consider the dynamics of the expected benefits, current alternatives and unknown risks. We suggest joint microbiome stewardship involving existing scientific networks (for example, the beneficial microorganisms for marine organisms network) for the rapid exchange of protocols, results, strategies and resources, together with microbiota repositories (inspired by microbiota vaults⁹⁰), which could catalyse the rapid development of probiotic applications to the environment. Carefully crafted production and safety policies in a system that stipulates speed without bureaucratic bottlenecks would provide companies with a clear framework to develop products that meet regulatory standards. Pilot-scale experiments could be proposed to provide baseline evidence before full-scale field tests. With sufficient data in place, legislators could work with researchers and companies to plan more widespread applications. Ultimately, we need to be able to reflect on our actions and know that we did not miss an opportunity to save our environment and the species critical to our survival.

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Author contributions

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Competing interests

The authors declare no competing interests.

Additional information

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